Letter to the Editor

Correlation Between Drug Exposure and Major Malformations

To the Editor:

We have read with great interest the paper by Queißer-Luft et al. [1996] on the correlation between drug exposure and major malformations, and we would like to comment on the following aspects.

First, the selection of the control group is not clearly explained. The authors stated that "controls consisted of all healthy newborns (n = 9,682) without any major or minor malformations." Thus, since the serial examination included 20,248 infants and only 1,472 were identified as cases, it is not clearly understood why the controls were only and precisely 9,682. So, it is not possible to know if the selection of controls may have produced some bias.

There was not sufficient and clear discussion on the limitations of the study, either on possible confounders (such as maternal diseases, fever, maternal age . . . which were not controlled) or on other biases (such as selection of controls). As an example, we can take the situation for insulin, which we consider to be important. It is well known that maternal diabetes mellitus is a teratogen which produces anomalies of the musculoskeletal system among others [Kučera, 1971; Martínez-Frías, 1994]. Queißer-Luft et al. [1996] did not control the maternal diabetes effect on the analysis, so it is not possible to attribute their results to the insulin treatment. However, the authors stated in the discussion "the combination of major malformations and the administration of insulin cannot be completely disregarded, but most authors view diabetes mellitus and not insulin as a risk factor." We disagree with their suggestion on the possible effect of insulin which, besides, is not demonstrated by their results, and which we consider to be confounded by maternal diabetes. In the same paragraph, they cited different anomalies that have been reported in the literature and concluded, "Results obtained by our study therefore corroborate those reported in the literature." This is rather confusing since the literature that they quoted did not show the relationship between insulin and those malformations but between maternal diabetes and those malformations, while they interpreted their results as possibly attributed to the treatment with insulin. At present, there is enough evidence to consider that insulin is not a teratogen, and that it is the only way that we have to reduce the risk of maternal diabetes.

The authors did not give any explanation for the observed association between chromosome aberrations (which are prezygotic problems) and some drugs used during gestation. We believe that some bias could be the reason for the correlation between chromosome alterations and some types of medication during pregnancy. Thus, this could be an indication that the same bias could account for other results.

The analysis was done using broad categories of drugs (i.e., antibiotics, antiallergics), and not all of the drugs included in each category are related to major malformations. From the way in which the results are reported, some physicians could conclude that all the drugs included in some groups (i.e., antiallergics) are teratogenic, which in our opinion may be a serious problem.

Finally, the authors stated that "correlations were established between . . ." and reported all the results with odd ratios (ORs) over 1, although most of them were not statistically significant. This may also be misunderstood by nonexpert readers.

In our opinion, we should be very cautious with the presentation and results on crude analysis (without controlling biases and confounders) of broad categories of drugs and malformations, even when the results are statistically significant. The reason is because these crude analyses, which have only heuristic utility, could be wrongly interpreted by clinicians who are not expert in evaluating risks, and could unjustifiably introduce some confusion in the always difficult pharmacologic treatment of pregnant women.

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M.L. Martínez-Frías*
E. Rodríguez-Pinilla
E. Bermejo
ECEMC and Departamento de Farmacologia
Facultad de Medicina
Universidad Complutense
Madrid, Spain

*Correspondence to: Dr. M.L. Martínez-Frías, ECEMC, Facultad de Medicina, Universidad Complutense, 28040, Madrid, Spain.

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